

# Progressive arm and leg stiffness in a patient with chronic renal impairment

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## SUMMARY

**Background** A 60-year-old white woman with a history of breast cancer, autoimmune hemolytic anemia, type 2 diabetes mellitus, peripheral vascular disease, and chronic renal insufficiency presented with stiffness in her arms and legs of 3 months' duration. She had undergone multiple MRI and magnetic resonance angiography examinations with gadolinium-containing contrast media over the last 2 years.

**Investigations** Complete physical examination including thorough skin examination; laboratory examinations including CBC, urinalysis, serum creatinine, protein electrophoresis and C-reactive protein; antinuclear antibody assay; Westergren erythrocyte sedimentation rate; and an excisional skin biopsy.

**Diagnosis** Nephrogenic systemic fibrosis (also known as nephrogenic fibrosing dermatopathy).

**Management** Symptomatic treatment, physical therapy, and a brief trial of imatinib mesylate.

**KEYWORDS** gadolinium, imatinib mesylate, MRI, nephrogenic systemic fibrosis, nephrogenic fibrosing dermatopathy

## CME

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### Learning objectives

Upon completion of this activity, participants should be able to:

- 1 Identify risk factors for nephrogenic systemic fibrosis (NSF).
- 2 Describe the anatomical distribution of skin changes associated with NSF.
- 3 Specify histopathological changes associated with NSF.
- 4 Describe treatment for NSF.

### Competing interests

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## THE CASE

A 60-year-old white woman presented to a rheumatology clinic with a chief complaint of increasing stiffness and skin thickening in her arms and legs, which had started 3 months before her presentation. Her medical history was notable for type 2 diabetes mellitus, coronary artery disease, hypertension, peripheral vascular disease, autoimmune hemolytic anemia, chronic renal insufficiency and early stage breast cancer. For the previous 2 years, the patient's serum levels of creatinine had ranged between 159–177  $\mu\text{mol/l}$  (normal 62–115  $\mu\text{mol/l}$ ) and her estimated glomerular filtration rate had been around 30  $\text{ml/min/1.73 m}^2$  (normal  $>60 \text{ ml/min/1.73 m}^2$ ).

The patient had undergone right femoropopliteal bypass surgery for peripheral vascular disease 9 years earlier. Several related surgeries on

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**Table 1** Results of laboratory studies.

Laboratory test	Result	Normal
Hematocrit (%)	30.3	36–48
Reticulocyte count (%)	3.4	0.6–2.8
Eosinophil count (per $\mu$ l)	210	0–500
Erythrocyte sedimentation rate (mm/h)	97	0–18
C-reactive protein (mg/l)	7.6	1.0–3.0
Ferritin (pmol/l)	3,751	23–391
Creatinine ( $\mu$ mol/l)	153	62–115
Estimated glomerular filtration rate (ml/min/1.73 m <sup>2</sup> )	28	>60
Urinalysis	Negative	Negative
Total protein (g/l)	74	60–80
Albumin (g/l)	36	37–54
Serum protein electrophoresis	Normal	Normal
Antinuclear antibody	Negative	Negative
Anti-Ro/SSA, anti-La/SSB, anti-Sm, anti-ribonucleoprotein antibodies	Negative	Negative
Anti-Scl 70	Negative	Negative
Creatine kinase (U/l)	32	27–218
Hemoglobin A1c (%)	5.0	4.2–5.8

her lower extremities were done subsequently, the latest being a left above-knee amputation 6 months before presentation. Over the previous 2 years the patient had had six MRI or magnetic resonance angiography examinations for peripheral vascular disease. Five of these exams included gadolinium-containing contrast media (total dose 105 ml of MultiHance® [Bracco International BV, Amsterdam, The Netherlands] and 60 ml of Magnevist® [Berlex Laboratories, Montville, NJ]).

The patient's musculoskeletal symptoms had started 1 month after her last MRI exam with contrast media. She first experienced difficulty in walking because of stiffness and skin tightening, which started in her right lower leg, then gradually progressed to both of her thighs and upper extremities. The skin of her face, hands and feet was not involved. She denied any warmth or swelling in her joints. She had not been treated with erythropoietin for anemia. She had not been exposed to chemicals such as vinyl chloride, benzene, or toluene. She had no Raynaud's phenomenon, photosensitivity, mucosal ulcerations, skin rash or nodules. She denied cough, dyspnea, reflux symptoms, or gastrointestinal bleeding. Her medications included hydralazine,

isosorbide dinitrate, amlodipine, clonidine, aspirin, furosemide, gabapentin, and insulin. She was not taking any over-the-counter medications or herbal supplements.

On physical examination, the patient was in no acute distress. Her blood pressure was 120/80 mmHg, pulse rate 70 beats/min, respiration rate 16 breaths/min, body temperature 97°F, and oxygen saturation 97% in room air. The skin of her right leg, left leg stump, and upper arms was waxy, tight, and hyperpigmented. The skin of her face, hands, feet and trunk was normal. Her chest was clear to auscultation and percussion. A cardiovascular examination revealed a grade 1/6 systolic flow murmur at the left sternal border. The results of a joint exam were normal except for an 80° flexion contracture of her right knee. Distal and proximal muscle strength was normal bilaterally. Results of laboratory studies are shown in Table 1. Abnormal results included a Westergren erythrocyte sedimentation rate of 97 mm/h (normal 0–18 mm/h), high-sensitivity C-reactive protein levels of 7.6 mg/dl (normal 1.0–3.0 mg/dl) and ferritin of 3751 pmol/l (normal 23–391 pmol/l). These markers had all been elevated over the last several years.

An excisional skin biopsy sample of the patient's right upper arm showed deep dermal fibrosis with extension into the superficial subcutaneous tissue (Figure 1A). Areas of fibrosis were associated with increased proliferation of fibroblasts (Figure 1B). No substantial inflammation was seen. A colloidal iron stain was positive and CD34 immunostaining highlighted the fibroblastic proliferation (Figure 1C,D).

A diagnosis of nephrogenic systemic fibrosis (NSF) was made, and a trial of 400 mg of imatinib mesylate was initiated but was stopped after the first dose because of gastrointestinal intolerance. The patient subsequently received oral analgesics and extensive physical therapy. Three months after diagnosis, her skin thickness and the extent of limb stiffness had improved slightly. The patient receives ongoing symptomatic treatment, and is reassessed every 2 months.

**DISCUSSION OF DIAGNOSIS**

This Case Study illustrates the differential diagnosis and management of a fibrosing skin syndrome in a patient with multiple medical problems, which required a detailed clinical history, pertinent laboratory tests and the examination of the skin pathology. It also demonstrates

the progressively debilitating nature of NSF, a fibrosing disorder first described less than a decade ago.

In 2000, Cowper *et al.*<sup>1</sup> reported the entity of rapidly progressing thickening and hardening of the skin associated with hyperpigmentation in hemodialysis patients (Figure 2), and in 2002 the US Centers for Disease Control and Prevention issued a public health alert for this disease. Since that time, the disorder has been increasingly recognized and its full spectrum and outcomes are now better appreciated. Initially named NFD (nephrogenic fibrosing dermatopathy), NSF seems to be a new systemic disorder that has its most prominent and visible effects in the skin. No case has been identified before early 1997 and it has been seen exclusively in individuals with renal disease. Nevertheless, the duration and type of kidney disease do not seem to be related to the incidence of NSF. There is no solid evidence that NSF is caused by medications, an infectious agent, or by dialysis *per se*.<sup>2</sup> The initiation of erythropoietin, especially at high doses, has been suggested as a trigger for NSF,<sup>3</sup> but the most compelling risk factor seems to be exposure to the gadolinium-containing contrast media (GCCM) used in MRI or magnetic resonance angiography.<sup>4–6</sup> In one report, the median time from GCCM exposure to the first clinical signs of NSF was 25 days (range 2–75 days).<sup>7</sup> Furthermore, gadolinium has been demonstrated in skin specimens of patients with NSF.<sup>8</sup> In a study employing only clinical criteria for NSF diagnosis (without skin biopsy results), cutaneous changes characteristic of NSF were discovered in 30% of GCCM-exposed patients with end-stage renal disease (ESRD).<sup>6</sup> A population-based study of patients with ESRD revealed that each radiologic study using gadolinium was associated with a 2.4% risk of developing NSF,<sup>5</sup> and further studies confirmed that the dose of the contrast agent or number of GCCM-enhanced MRI exams undergone increases the likelihood of developing NSF.<sup>9,10</sup> Interestingly, one study reported that patients with chronic renal impairment exposed to GCCM developed NSF only if they had experienced a recent inflammatory event such as surgery or infection.<sup>9</sup> The patient in this illustrative Case Study had some of these predispositions. It is likely that her elevated erythrocyte sedimentation rate or C-reactive protein values could be associated with an underlying illness other than NSF; these inflammatory markers had been chronically

elevated for years, preceding her musculoskeletal symptoms at presentation.

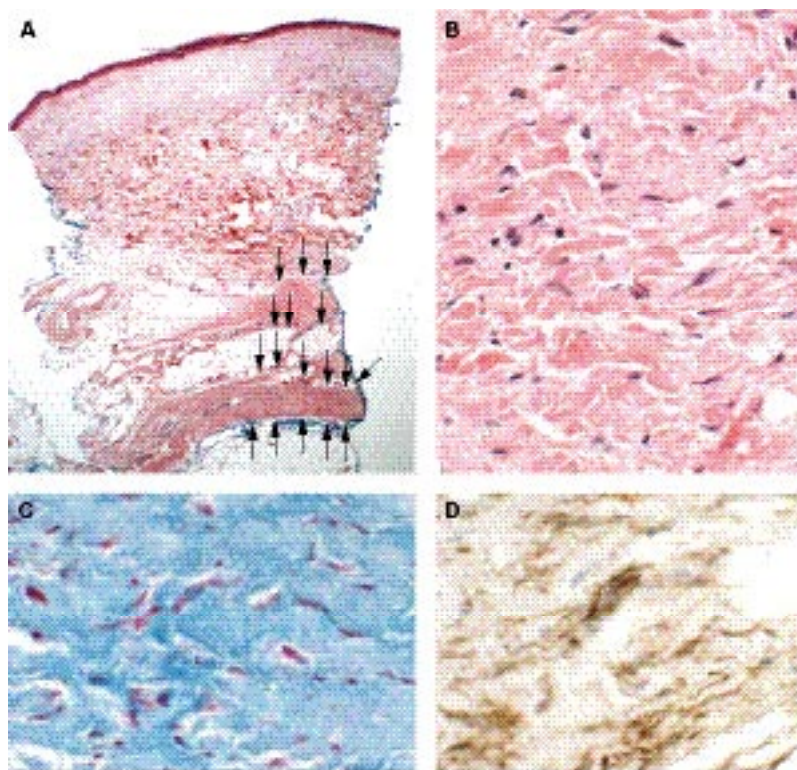
Skin lesions in NSF primarily involve the lower extremities more often than the upper extremities and the trunk; the hands and feet are mostly spared, which differentiates the condition from scleroderma. The face and neck are rarely involved. If edema is present, it gradually resolves on its own but leaves brawny, indurated plaques that progress to a 'peau d'orange' appearance, and skin thickening that leads to joint contractures. NSF can also cause systemic fibrosis in the skeletal muscles, myocardium, and lungs.<sup>11</sup>

Histopathologic tissue examination is considered the gold standard for establishing a diagnosis of NSF.<sup>12,13</sup> Typical changes include thickening of the dermis with bands of fibrosis extending into the subcutaneous adipose tissue.<sup>14</sup> The composite fibroblasts within bands of fibrosis are often oriented parallel to the overlying epidermis.<sup>15</sup> Other features of NSF can include the presence of stellate-like cells or osteoclast-like giant cells.<sup>16</sup> In some cases, stromal mucin has been described but the appearance of this is often subtle and not appreciated by routine hematoxylin and eosin staining; a mucin or colloidal iron stain might be required to identify this feature. Skin changes often involve the full thickness of the dermis; however, pathologic findings can be centered on the deep dermis and superficial subcutaneous tissue as in this Case Study. A deep-tissue biopsy would, therefore, be necessary.<sup>2</sup> Histologic findings are often extremely subtle and nonspecific, and require careful clinicopathological correlation to establish a diagnosis. Some patients might need multiple biopsies to identify diagnostic histopathologic changes.

A potential mechanism for the pathogenesis of NSF involves circulating CD34<sup>+</sup> fibrocytes: these bone marrow-derived, spindle-shaped cells are recruited in response to tissue injury, and perhaps endothelial disruption.<sup>16</sup> Fibrocytes produce inflammatory cytokines, chemokines, and growth and angiogenic factors. Furthermore, increased expression of transforming growth factor- $\beta$ 1 has been identified in the skin, fascia, and striated muscle of patients with NSF, which in turn might contribute to the increased deposition of extracellular matrix.<sup>17</sup>

#### DIFFERENTIAL DIAGNOSIS

Patients with ESRD generally have a variety of cutaneous manifestations such as changes secondary to pruritis, perforating folliculitis,



**Figure 1** Histopathology of deep-skin biopsy samples of the case patient. (A) At low-power magnification (magnification  $\times 20$ ), bands of fibrotic tissue can be seen at the base of the dermis with extension into the superficial subcutaneous tissue (arrows). (B) An image at high magnification (magnification  $\times 400$ ) shows a fibrous band of tissue with increased numbers of fibroblasts. (C) Colloidal iron stain is positive with a blue reaction product. (D) An immunostain for CD34 highlights cells within the fibroblastic proliferation.

metastatic calcifications, and bullous dermatosis.<sup>13</sup> A list of the major differential diagnoses of NSF is shown in Box 1.<sup>12</sup> The main differential diagnoses considered in this case were NSF, scleromyxedema, systemic sclerosis, morphea, eosinophilic fasciitis,  $\beta_2$ -amyloidosis and paraneoplastic syndrome. Scleromyxedema is a chronic idiopathic disorder that produces indurated plaques, nodules, papules containing mucin, and fibrosis, mostly in the face. It is also associated with paraproteinemia. Skin lesions in systemic sclerosis are strikingly similar to those in NSF, showing thick, tight skin and pigmentation; however, systemic sclerosis also involves acrosclerosis with pitting scars and facial involvement, as well as visceral involvement and the presence of characteristic auto-antibodies. Skin changes in morphea tend to differ from those in NSF by the presence of an erythematous border, and the skin pathology of morphea demonstrates homogenized collagen in



**Figure 2** Cutaneous thickening and hardening with firm nodular lesions in the lower extremity. Reprinted from *The Lancet*, Vol. 356, Cowper SE *et al.*, Scleromyxoedema-like cutaneous diseases in renal-dialysis patients, pages 785–790, Copyright (2000), with permission from Elsevier.

the absence of mucin. Patients with eosinophilic fasciitis can also present with induration of the distal extremities and contractures with loss of mobility, as well as peripheral blood eosinophilia and hypergammaglobulinemia. Biopsy results of eosinophilic fasciitis show dermal and subcutaneous sclerosis associated with inflammation with variable numbers of lymphocytes, plasma cells, and eosinophils. By contrast, NSF is not typically associated with significant inflammation. Although ‘burnt out’ lesions of morphea or scleroderma might have only minimal inflammation, the presence of homogenization of dermal collagen helps to distinguish these lesions from those of NSF. Skin abnormalities related to diabetes mellitus should also be considered in the differential diagnosis of thickened skin. Patients with scleredema diabeticorum can present with waxy thickened skin on the neck and upper back and limited joint mobility and sclerodactyly caused by glycosaminoglycan deposition. Necrobiosis lipoidica diabeticorum is associated with well-circumscribed, waxy, initially indurated and later atrophic plaques on the legs. Both conditions can be ruled out by the distribution of the lesion and the histopathology of the patient’s skin biopsy results.

**Box 1** Differential diagnosis for nephrogenic systemic fibrosis.

Scleromyxedema  
 Eosinophilia–myalgia syndrome  
 Eosinophilic fasciitis (Shulman syndrome)  
 Systemic sclerosis or morphea  
 Porphyria cutanea tarda  
 Fibroblastic rheumatism  
 Scleredema  
 Spanish toxic oil syndrome  
 Vinyl chloride exposure  
 $\beta_2$ -Microglobulin amyloidosis  
 Dermatofibrosarcoma protuberans

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**TREATMENT AND MANAGEMENT**

There is no tested, effective treatment for NSF. In several cases the skin component of the disease has reversed following renal transplantation.<sup>18</sup> Other case reports have demonstrated the benefit of extracorporeal photopheresis.<sup>19</sup> Plasmapheresis, high-dose intravenous immunoglobulin, steroids, and thalidomide need further studies to test their value. The tyrosine kinase inhibitor imatinib mesylate blocks the signaling pathway of transforming growth factor- $\beta$ 1, which is found at increased levels in tissues of patients with NSF and in animal models of pulmonary fibrosis.<sup>17,20,21</sup> A pilot study of daily 400 mg imatinib mesylate in two patients with NSF showed substantial improvement in the modified Rodnan skin score and flexion contractures after 15 weeks of treatment.<sup>21</sup> A clinical trial of imatinib mesylate for NSF is now underway (J Kay; personal communication).

Although there is no cure for NSF, general supportive measures can be useful. In addition to pain control, patients should receive vigorous active and passive range of motion exercises to improve or prevent joint contractures.

The association between NSF and GCCM has led to the development of guidelines for the use of GCCM in patients with renal insufficiency,<sup>10,22,23</sup> and in June 2006 the FDA issued an advisory to healthcare professionals (Box 2).<sup>23</sup> It is still unclear whether hemodialysis following exposure to GCCM could prevent NSF in high-risk patients. Outside the US, the restrictions on the use of GCCM agents in patients with chronic kidney disease are even stronger: in Europe, gadodiamide (Omniscan® [GE Healthcare, Oslo, Norway]),

**Box 2** FDA guidelines for the use of gadolinium in patients with renal impairment.<sup>23</sup>

- Become familiar with the patient populations who are known to be at risk for NSF
  - Acute or chronic severe renal insufficiency (GFR <30 ml/min/1.73 m<sup>2</sup>)
  - Acute renal dysfunction resulting from hepato-renal syndrome or in the perioperative liver transplantation period
- Avoid using GCCM in patients with known risks of developing NSF unless the diagnostic information is essential and cannot be obtained with non-contrast enhanced MRI or other diagnostic procedures
- Prior to administering GCCM, evaluate patients for renal dysfunction by assessing their renal function, either by obtaining a medical history or by conducting laboratory tests
- When administering GCCM, do not exceed the recommended GCCM dose in product labeling and allow a sufficient period of time for elimination of the agent from the body before any re-administration
- For patients receiving hemodialysis, consider hemodialysis promptly following administration of GCCM
- Report possible cases of NSF to the FDA through the FDA's MedWatch program

Abbreviations: GCCM, gadolinium-containing contrast media; GFR, glomerular filtration rate; NSF, nephrogenic systemic fibrosis.

gadopentetate dimeglumine (Magnevist®), and gadoversetamide (OptiMARK® [Mallinckrodt, St Louis, MO]) were banned in patients with renal disease in spring 2007.<sup>22</sup>

**CONCLUSIONS**

NSF (previously called NFD) is a systemic fibrosis disorder exclusively detected in patients with renal insufficiency. The precise etiology of the disorder is unknown but GCCM compounds have a particularly strong association with NSF. Patients with NSF present with rapidly progressive skin thickening and pigmentation—mainly in the extremities—that leads to substantial functional disability and increased morbidity. With strong clinical suspicion and awareness of the disorder, a detailed clinical history including history of exposure to GCCM should be obtained along with a deep-skin biopsy. The

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**Competing interests**

The authors declared no competing interests.

proximal distribution of the skin involvement, lack of paraproteinemia, absence of Raynaud's phenomenon, anti-Scl 70 or anti-centromere autoantibodies, and diagnostic skin histopathology are important features for a diagnosis of NSF.

Effective treatment modalities are still under investigation; pain control and aggressive physical therapy are the mainstay treatment. The primary goal is to prevent NSF; one way to do this is by avoiding unnecessary exposure to GCCM for patients with risk factors for NSF, especially those who have acute or chronic renal insufficiency with a glomerular filtration rate of less than 30 ml/min/1.73 m<sup>2</sup>.

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